

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of : Holmaas *et al.*
Application No. : 10/560,497
Filing Date : December 12, 2005
Art Unit : 1621
Title : Process for Iohexol Manufacture

Docket No. : PN0324

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APPEAL BRIEF

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I. REAL PARTY IN INTEREST

The real party in interest in this Appeal is Amersham Health AS (now GE Healthcare AS, a part of General Electric “GE”).

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences related to the instant appeal.

III. STATUS OF CLAIMS

Claims 1-21 are pending in this application. The Examiner has rejected all of these claims. Claims 1-21 as amended during prosecution are reproduced in the **Claims Appendix** attached hereto. Appellants are appealing the rejection of Claims 1-21.

IV. STATUS OF AMENDMENTS

A final Office Action was mailed on October 9, 2008. No claims have been amended thereafter.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 1 describes a process for the production of iohexol comprising alkylating 5-(acetamido)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide with a 2,3-dihydroxypropylating agent in the presence of a base and of a solvent which solvent comprises a C₁-C₅-monoalkylether of a C₃-C₁₀ alkylene-glycol.

Support for this claim can be found on page 3, line 23 to line 27 of the specification.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues for review in this appeal arise from an Office Action dated October 9, 2008. The Examiner rejected claims 1-21 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,948,940 to Malthe-Sorensen et al. (“Malthe-Sorensen”). Therefore, the issue in this appeal is:

1. Whether Malthe-Sorensen discloses, teaches, or suggests the elements of claims 1-21?

VII. ARGUMENT

The Examiner rejected Claims 1-21 under 35 U.S.C. § 103 (a) as allegedly being unpatentable over U.S. Patent No. 5,948,940 to Malthe-Sorensen et al. (“Malthe-Sorensen”).

Appellants respectfully request that The Board of Patent Appeals and Interferences (“Board”) should reverse the Examiner’s rejection for the reasons set forth below.

A. The Examiner’s Rejection of Claims 1-21 Should be Reversed Since Malthe-Sorensen Fails to Disclose, Teach or Suggest All the Elements of Claims 1-21.

The Examiner’s Rejections of Claims 1-21 should be reversed since Malthe-Sorensen fails to disclose, teach, or suggest all the elements of claims 1-21.

In the present invention Appellants disclose a process for the production of iohexol

comprising alkylating 5-(acetamido)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide with a 2,3-dihydroxypropylating agent in the presence of a base and in the presence of a solvent which solvent comprises a C₁-C₅-monoalkylether of a C₃-C₁₀-alkylene-glycol. Preferably the solvent is 1-methoxy-2-propanol.

“Malthe-Sorensen” describes a process for the production of iohexol using 2-methoxy-ethanol as a solvent. The objective of the present invention is to find an alternative solvent to the one described in Malthe-Sorensen and other prior art references for the above-mentioned manufacturing process thus surprisingly improving the manufacture of iohexol (please see page 3, lines 9-20 of the specification).

In previous Office Actions dated October 9, 2008 and April 14, 2008, the Examiner holds that Malthe-Sorensen clearly suggests that for one having ordinary skill in the art it is routine for a skilled artisan to use art recognizing alternative solvents, and that it would have been obvious to a person skilled in the art to use 1-methoxy-2-propanol in Malthe-Sorensen.

Appellants respectfully disagree. Malthe-Sorensen describes a process for the production of iohexol where the solvent used is 2-methoxy-ethanol. Malthe-Sorensen does not teach, describe, or suggest using any other solvent other than 2-methoxy-ethanol. There are no indications in Malthe-Sorensen regarding which solvent might be used as an alternative solvent and there are not even indications that alternative solvents could be used. Accordingly, Malthe-Sorensen clearly suggests the use of 2-methoxy-ethanol and no other alternatives.

Additionally, Appellants are the assignee of Malthe-Sorensen and if it would have been

obvious to use other solvents other than 2-methoxy-ethanol, those solvents would clearly have been incorporated. The fact that Malthe-Sorensen does not speak in general of solvents, but only of 2-methoxy-ethanol specifically, clearly does not imply “suggesting the use of similar solvents”, rather to the contrary. Appellants also wish to remind the Examiner that “the prior art itself must provide a motivation or reason for the worker in the art, without the benefit of the Applicant’s specification, to make necessary changes in the reference device”. See, *Ex parte Chicago Rawhide Manufacturing Co.*, 226 U.S.P.Q. 438 (PTO Bd. App. 1984).

Disregarding the fact that Malthe-Sorensen does not teach, disclose, or suggest the use of alternative solvents, one skilled in the art would in fact not have a reasonable expectation of success when using 1-methoxy-2-propanol as solvent in the process.

In addition to the subject matter described in Malthe-Sorensen it was known from WO02/083623, as discussed in the present specification, page 2, lines 1-2, to use 1-methoxy-2-propanol as solvent in the purification by recrystallization of iohexol.

The fact that a solvent is known for its use as the dominant solvent in the crystallisation step of the same process would clearly teach away from using the same in the alkylation step. ‘Teaching away’ simply means teaching a solution that would not lead to the claimed subject matter. As noted by the Federal Circuit:

A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.

(emphasis added).

Para-Ordnance Mfg. v. SGS Importers Int'l, 73 F.3d 1085 (Fed. Cir. 1995).

Knowing that 1-methoxy-2-propanol is used as the solvent in the purification by recrystallization of iohexol, one skilled in the art would not expect that the same solvent could also be used in the alkylation step. The reason for this is that in the alkylation step it is required that the solvent shows good solubility for 5-(acetamido)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide and that the product (iohexol) does not precipitate during the reaction, whereas in the purification step the solvent used should show little solubility for the product (iohexol). A person skilled in the art would therefore not expect that 1-methoxy-2-propanol could successfully be used as solvent in both the alkylation and the purification step, and would not think or suggest using 1-methoxy-2-propanol as an alternative to 2-methoxy-ethanol in the production described by Malthe-Sorensen. Malthe-Sorensen does describe using 2-methoxy-ethanol as a solvent in both the alkylation and in the purification step, however, the solvent mixture only comprises a very small amount of 2-methoxy-ethanol in the purification step, see claim 1.

In addition to the arguments discussed above other aspects supported the belief that 1-methoxy-2-propanol could not be used as solvent in the current process, thereby making it unobvious to try. These aspects are also addressed in the Declaration set forth below from one of the inventors, Ole Magne Homestad. In short, 2-choxyethanol was considered as an alternative solvent but was found to have too poor solubility. Knowing that 1-methoxy-2-propanol was even less polar there were no reason to pursue 1-methoxy-2-propanol as solvent. In addition,

one could consider adding co-solvents to improve solubility, but knowing that such addition to 2-methoxy-ethanol used in the current process worsen the selectivity only supported the belief that 1-methoxy-2-propanol could not be used.

The Examiner has stated in the issued Office Actions that it would have been obvious to use 1-methoxy-2-propanol in Malthe-Sorensen with a reasonable expectation of success without giving any further reasons for that in view of the applicants' arguments to the contrary.

The Examiner further holds that "applicants allege that even though the solvent in question only differs by one carbon, they act very differently and attempt to demonstrate so by way of comparative data shown in table 1 and 2. However, results in tables 1 and 2, such as yield/purity of the product and the amount of other impurities, are not significantly different from the closest prior art". The Examiner further states that the Appellants have not shown unexpected and beneficial results in a beneficial side by side comparison with the closest prior art.

Appellants respectfully submit that examples 1-3 in the specification and tables 1 and 2 were not introduced to demonstrate that solvents only differ by one carbon can act differently. The examples in the specification and tables were introduced to demonstrate that surprisingly and unexpectedly 1-methoxy-2-propanol could be used as an alternative solvent to 2-methoxy-ethanol showing the same, and even slightly better, purity of iohexol. The motivation behind the invention was to find, if possible, an alternative to 2-methoxy-ethanol as disclosed in Malthe-Sorensen.

Additionally, to expect one skilled in the art reading Malthe-Sorensen to try 1-methoxy-2-propanol as an alternative solvent would clearly involve using hindsight. The skilled artisan would have to:

1. Attempt to use alternative solvents even though Malthe-Sorensen specifically concerns the use of 2-methoxy-ethanol and in no way suggests that other solvents might work;
2. Discover that 1-methoxy-2-propanol is an alternative solvent among a vast number of compounds; and
3. Disregard the known facts indicating that 1-methoxy-2-propanol would not work as a solvent in the alkylation step.

Appellants therefore respectfully request that the Board should reverse the Examiner's obviousness rejection of claims 1-21 since Malthe-Sorensen Fail to Disclose, Teach or Suggest All the Elements of Claims 1-21.

CONCLUSION

In view of the foregoing, Appellants respectfully request that the Board reverse the rejections of Claims 1-21 as set forth in the Office Action mailed October 9, 2008, that the Board allow the pending claims since they are in condition for allowance, and that the Board grant any other relief as it deems proper.

Dated: April 3, 2009

Respectfully submitted,

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VIII. CLAIMS APPENDIX

1. A process for the production of iohexol comprising alkylating 5-(acetamido)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide with a 2,3-dihydroxypropylating agent in the presence of a base and of a solvent which solvent comprises a C₁-C₅-monoalkylether of a C₃-C₁₀ alkylene-glycol.

1. A process as claimed in claim 1 wherein said C₁-C₅-monoalkylether of a C₃-C₁₀ alkylene-glycol is 1-methoxy-2-propanol.
2. A process as claimed in claim 1 further comprising one or more co-solvents.
3. A process as claimed in claim 3 wherein said co-solvents comprise C₁-C₄ alkanols and/or water.
4. A process as claimed in claim 3 wherein said solvent comprises 1-methoxy-2-propanol and 0-40 volume% of methanol.
5. A process as claimed in claim 3 wherein said solvent comprises 1-methoxy-2-propanol and 0-20 volume% of water.
6. A process as claimed in claim 1 wherein said solvent is used in an amount of 0.5 to 5 ml per gram 5-Acetamide.
7. A process as claimed in claim 1 further comprising purifying the crude iohexol obtained from the N-alkylation reaction using a solvent comprising a C₁-C₅-monoalkylether of a C₃-C₁₀ alkylene-glycol.
8. A process as claimed in claim 8 wherein the C₁-C₅-monoalkylether of a C₃-C₁₀ alkylene-glycol is the same C₁-C₅-monoalkylether of a C₃-C₁₀ alkylene as used in the N-alkylation process.

9. A process as claimed in claim 8 wherein said purification the C₁-C₅-monoalkylether of a C₃-C₁₀ alkylene-glycol is 1-methoxy-2-propanol.
10. A process as claimed in claim 8 wherein said purification the solvent further comprises one or more co-solvents.
11. A process as claimed in claim 11 wherein said co-solvent comprises C₁-C₄ alkanols.
12. A process as claimed in claim 9 wherein the amount of said solvent is adjusted to 1.5 to 8 ml of the C₁-C₅-monoalkylether of a C₃-C₁₀ alkylene-glycol /g iohexol, to 0-1 ml C₁-C₄ alkanol/g iohexol, and to 0.001-0.3 ml water/g iohexol.
13. A process as claimed in claim 8 wherein the purification is performed by crystallising the iohexol from said solvent and then separating the crystals from said solvent.
14. A process as claimed in claim 8 wherein the salt content in the reaction mixture of the alkylation reaction is reduced prior to the purification step.
15. A process as claimed in claim 8 wherein the water content in the reaction mixture of the alkylation reaction is reduced prior to the crystallisation step preferably by azeotropic distillation.
16. A process as claimed in claim 8 wherein the crystalline iohexol is washed with isopropanol and dried.
17. A process as claimed in claim 4 wherein said C₁-C₄ alkanol is methanol.
18. A process as claimed in claim 7 wherein said solvent is used in an amount of 0.7 to 3 ml per gram 5-Acetamide.

19. A process as claimed in claim 7 wherein said solvent is used in an amount of 0.9 to 1.0 ml per gram 5-Acetamide.

20. A process as claimed in claim 12 wherein said co-solvent comprises methanol.

IX. EVIDENCE APPENDIX

Appellants hereby present the following patent:

U.S. Patent No. 5,948,940 to (“Malthe-Sorensen”).

This is the evidence relied upon by the Examiner for rejection of appealed Claims 1-21 in the final Office Action dated October 9, 2008.

X. RELATED PROCEEDINGS APPENDIX

There are no other appeals or interferences related to the instant appeal.

XI.

37 CFR 1.132 Declaration

In accordance with rule 37 CFR 1.112, I, Ole Magne Homestad, do hereby declare that:

I am inventor of said invention and currently reside in Sor-Audnedal, Norway.

Reference is made to the Office Actions dated 11/21/2006, 04/26/2007, 10/29/2007 and 04/14/2008.

In the present N-alkylation step of the synthesis of iohexol 2-methoxyethanol (2-ME) is used as solvent. When we searched for an alternative solvent to 2-ME, we considered the “nearest neighbour” of 2-ME, namely 2-ethoxyethanol. It was impossible to use this solvent due to solubility and selectivity. 1-methoxy-2-propanol (PM) was not considered since it was estimated to be even less polar than 2-ethoxyethanol.

To be able to use a solvent in the alkylation step it is necessary that NaOH is soluble. This is the case for 2-ME. Regarding PM, NaOH was not soluble and hence, it would be impossible to dissolve ‘541’ to obtain alkylation reaction conditions.

At first a modification of PM by adding co-solvents for increasing solubility of NaOH was not considered due to the assumption that such an addition would worsen selectivity of the reaction. This is true for 2-ME. It was therefore definitely not obvious to pursue this lead any further.

In summary it was not believed that PM was able to substitute 2-ME. This assumption was based on decades of experience with these processes and general chemical knowledge. It was consequently much unexpected that PM turned out to be a suitable replacement for 2-ME.

I declare under penalty of perjury pursuant to the laws of the United States of America that the foregoing is true and correct, and that this declaration was executed by me on 11th July 2008 at Spangereid, Norway.

-/Ole Magne Homestad/-----
Ole Magne Homestad